REMARKS

Reconsideration is respectfully requested. Claims 15-19 and 22-25 stand rejected. Claims 21 and 22 are canceled. Claims 26-30 are new. Support is found in the specification and claims as filed (see for example, Table 5 and column 6, lines 40-44).

With respect to all amendments and canceled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Objections to the Specification

The specification has been amended such that the paragraph at lines 17-31 of page 4 concludes with a period. Applicant respectfully requests withdrawal of this objection.

Claim Rejection Under 35 U.S.C. § 112, first paragraph

Enablement

Claims 15-19 and 22-24 stand rejected under 35 U.S.C. §112, first paragraph, allegedly for lack of enablement.

The position outlined in the Office Action appears to be that while the specification is enabling for the use of amonafide in conjunction with . . . homoharringtonine . . . for the treatment of fibrosarcoma, it is not enabling for the treatment of solid tumors. Applicants respectfully traverse.

As noted previously, the Examiner asserts that

> [In] order to be enabled to practice the present invention, the skilled artisan would have to accept that by administering the presently claimed combination of active agents, all solid tumors known in the art could be treated. . . . Because the specification fails to direct the skilled artisan as to which other tumors aside from fibrosarcoma are known to be sensitive to such a composition, and especially in consideration of the highly complex nature of tumors and cancer in general, the specification, which lacks an objective showing of which solid tumors other than fibrosarcoma could be effectively treated using the claimed combination of active agents, is viewed as lacking an enabling disclosure of the same.
> [Pages 11-12 of the Office Action]

Applicants respectfully disagree and respectfully point out that some experimentation, even if complex, is allowable under 35 U.S.C. §112, first paragraph. MPEP §2164.01 (The fact that experimentation may be

complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Intl Trade Comm'n 1983), affd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976)). As previously described, the RIF-1 fibrosarcoma model utilized in Example 2 of the instant specification has been used for decades as an established tumor model. Therefore, one of ordinary skill in the art would expect that the combination of HHT and amonafide would be efficacious against other solid tumors. That is, one of skill in the art would view successful experiments with the RIF-1 model system as exemplary of success in other tumor systems. Therefore, it would not require undue experimentation to successfully use HHT and amonafide on other solid tumors. While some experimentation would be required, Applicants submit that the amount of experimentation would not be undue. Accordingly, the specification is enabling for claim 15 and those claims depending therefrom as directed to the treatment of solid tumor.

In addition, Applicants note that claim 19 and new claims 26-28 recite that the anticancer effect of the treatment with amonafide and homoharringtonine is greater than that for amonafide or homoharringtonine alone (or in the case of claims 26-28 the effect of the combination is greater than that of homoharringtonine alone). Applicants note that as of the effective date of the present application, homoharringtonine sensitive solid tumors were known (see, for example, Jiang et al. Comparative *in vitro* Antitumor Activity of Homoharringtonine and Harringtonine Against Clonogenic Human Tumor Cells; *Invest. New Drugs* 1, 021-025 (1983) (cited by the Examiner)). Thus, identification of solid tumors that were sensitive to homoharringtonine was within the skill of one of ordinary skill in the art. The present application, however, extended this work by demonstrating that the effectiveness of HHT as a chemotherapeutic was increased when used in combination with amonafide. Thus, while the Examiner's position is that the claims are not enabled for the scope of treating any solid tumors, Applicants submit that one of skill in the art, following the teachings of the specification, would be capable of identifying tumors that were sensitive to HHT or amonafide. That is, while not every solid tumor will be sensitive to amonafide and HHT, the identification of solid tumors that are sensitive would not require undue experimentation.

Moreover, with respect to claims 19 and 26-30, Applicants submit that the scope of enablement necessary to support the claims is treatment of HHT sensitive tumors with amonafide and HHT (for

claims 19 and 26-28) and the treatment of amonafide sensitive tumors with HHT and amonafide (for claims 29-30). Applicants have demonstrated identification of HHT sensitive solid tumors (see Table 5 and column 7, lines 40-44) and also demonstrated increased effectiveness of amonafide and HHT in treating solid tumor (see Table 5 and page 4, lines 4-8 (paragraph [0049] of US Application Publication 2004/0047918). Similarly, Applicants have identified amonafide sensitive solid tumors and demonstrated increased effectiveness of amonafide and HHT in treating solid tumors (see Table 5, and throughout the specification). Given that the identification of HHT sensitive tumors was known in the art, Applicants submit that it would not require undue experimentation to identify solid tumors with increased sensitivity to amonafide and HHT. This, taken with knowledge of one of skill in the art regarding HHT sensitive tumors, clearly establishes that the claims are enabled. Applicants respectfully request the Examiner to withdraw this rejection.

Claim Rejection Under 35 U.S.C. 103(a)

Claims 15-18, 22-25 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Scheithauer et al. (*Breast Cancer Research and Therapeutics*, 20:63-67, 1991) (hereinafter "Scheithauer") in view of Jiang et al. (*Investigational New Drugs*, 1:21-25, 1983) (hereinafter "Jiang").

Applicants respectfully suggest that the references cited by the Examiner fail to support a *prima facie* case of obviousness for the claims as previously presented. To construct a *prima facie* case of obviousness, the cited references must meet three criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references) must teach or suggest all of the claim limitations. *In re Vaeck*, 947 F.2d 488, (Fed. Cir. 1991). As stated in the May 3, 2007 memorandum from Margaret A. Focarino to the USPTO Technology Center directors, these elements must still be met, even under the Supreme Court ruling for *KSR Int'l Co. v. Teleflex, Inc.*, (No. 04-1350 (U.S. Apr. 30, 2007)), and that "*in formulating a rejection under 35 U.S.C. §103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.*" Applicants respectfully submit that each of the required criteria set forth above have not been satisfied and thus, a *prima facie* case of obviousness has not been set forth.

1. Claim 15

Claim 15 recites "contacting said host with amonafide in conjunction with homoharringtonine." On page 20-21 of the Office Action, the Examiner cites Scheithauer as teaching "treatment of patients with advanced breast cancer . . . using amonafide" and Jiang as teaching that "homoharringtonine . . . was known in the art to demonstrate significant antitumor activity in solid tumors, including ovarian, endometrial and breast cancer, as well as sarcoma."

In addition, the Examiner cites the last sentence in Scheithauer, which reads "[amonafide] should therefore be considered for further evaluation and incorporation in combination chemotherapy." The Examiner argues that this provides the motivation to modify Scheithauer:

> One of ordinary skill in the art would have been motivated to use amonafide in conjunction with homoharringtonine for the treatment of breast cancer . . . since each was known separately in the art to have significant therapeutic activity in the treatment of breast tumors. Motivation to administer both compounds flows logically from this shared efficacy and the demonstration in the prior art that each had been previously administered for the same therapeutic endpoint.
> [Page 21-22 of the Office Action]

Applicant respectfully disagrees. Neither reference provides any suggestion or motivation to use amonafide in conjunction with homoharringtonine. M.P.E.P. §2143.01 I. provides that "obviousness can only be established . . . where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." Neither reference explicitly suggests treatment "with amonafide in conjunction with homoharringtonine" as required by claim 15. The test for an implicit suggestion is provided by the M.P.E.P as well.

> "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000).
> [Id.]

The last sentence in Scheithauer cited by the Examiner would not implicitly motivate a person of ordinary skill in the art to reach a treatment "with amonafide in conjunction with homoharringtonine." A myriad of possible agents exist that could be used in conjunction with amonafide. For example, a search of the Food and Drug Administration (FDA) website for pending clinical trials at www.clinicaltrials.gov yielded 659 hits using the key words "breast cancer." As such, no motivation or suggestion exists to select homoharringtonine from hundreds of possible anticancer agents to reach the present invention.

In addition, the Examiner argues that

> [A] common function of each of the compounds would have raised the reasonable expectation of success that the combination of both amonafide and homoharringtonine would have achieved, at a minimum, a potentiated antitumor effect, such that the effect of the agents when combined would have been greater than the effect achieved by either single agent alone .. .
> [Page 22 of the Office Action]

The Applicant respectfully disagrees. As discussed above, there is no motivation provided in either reference to reach a method of treatment "with amonafide in conjunction with homoharringtonine" as required by claim 15. Given the lack of motivation to modify the references, there is no reasonable expectation of success.

Moreover, even assuming the use of HHT and amonafide had been suggested in the treatment of solid tumors, such would have been unpredictable treatment and would not have provided a reasonable expectation of success. It was not until Applicant demonstrated that such combination therapy was effective that such treatment became predictable.

Claim 25

In addition, the Examiner asserts that the "composition comprising amonafide and homoharringtonine" of claim 25 is obvious because

> [The] motivation to administer the two compounds in a single formulation would have been *prima facie* obvious to one of ordinary skill in the art, since each was known to exhibit efficacy in the treatment of breast cancer and would have been reasonably expected to achieve a greater antitumor effect when combined than when given individually.
> [Page 22 of the Office Action, second paragraph]

However, as discussed above, there is no motivation provided in either reference to reach the method claims of the present invention because of the myriad number of agents that might be given in conjunction with amonafide. Similarly, there is no motivation in either reference to reach a "composition comprising amonafide and homoharringtonine," as required by claim 25.

The Examiner has failed to establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a). As such, the Applicant respectfully requests the withdrawal of this rejection.

Double Patenting Rejections

Applicants appreciate the Examiner's withdrawing the rejections over U.S. Patent No. 6,630,173, U.S. Application No. 11/067,074, and U.S. Application No. 10/625,866.

Claims 15-19 and 22-24 stand provisionally rejected as allegedly unpatentable under the judicially created doctrine of obviousness-type double patenting over pending claims 50-59 of U.S. Application No. 10/976,961. Pending claims 50-59 of 10/976,961 are directed to a "method of treating a subject with cancer comprising the step of administering to the subject an effective amount" of an amonafide analog. Claims 15-19 and 22-24 of the present invention are directed to methods of treatment "with amonafide in conjunction with homoharringtonine." Applicants respectfully submit that a method treatment that requires amonafide is distinct from a method that requires treatment with an amonafide analog. As such, the claims of the present invention are patentably distinct over 10/976,961.

Claim 25 stands provisionally rejected as allegedly unpatentable under the judicially created doctrine of obviousness-type double patenting over pending claims 42-44 of U.S. Application No. 10/976,961. Applicants respectfully traverse the rejection. Claims 42-44 recite a pharmaceutical composition comprising a naphthalimide analog. Claim 25 of the present invention requires a "pharmaceutical composition comprising amonafide and homoharringtonine." As such, claim 25 is patentably distinct.

Based on the foregoing, Applicant respectfully requests withdrawal of all double patenting rejections.

CONCLUSION

Applicants believe the present application is in condition for allowance. Early favorable communication thereof is respectfully requested. Please direct any calls in connection with this application to the undersigned at (415) 442-1216.

Respectfully submitted,
Morgan, Lewis & Bockius, LLP

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